IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
www.iosrphr.org Volume 5, Issue 4 (April 2015), PP. 44-49

Chronic Pneumonia: Update on Clinical Manifestations, Diagnosis and Therapy

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ABSTRACT: *Chronic pneumonia syndrome (CPS) has high fatality rate worldwide, economic cost in the United States, Europe and heavy burden of disease in the Asian countries. Older patients are at high risk of developing necrotizing pneumonia. Genetic factors play important role in manifestation of tuberculosis and disseminated cocciodioidomycoses among African and Asians. Occupation and hobbies do play an important role. Travelers to southeast Asia with abnormal radiography may be suffering from melioidosis.CPS is caused by Mycobacterium tuberculosis, nontuberculous mycobacteria, endemic fungi, cryptococcosis, and opportunistic infections like nocardiosis and aspergillosis. Clinical manifestations often nonspecific, including fever, chills, anorexia, weight loss, indicating chronic illness with pulmonary symptoms. Diagnosis by radiographic studies, high resolution CT(HRCT),position emission tomography, bronchoalveolar lavage(BAL),and CT guided transthoracic fine-needle aspiration(FNA).Empirical therapy based on epidemiologic, clinical, radiographic and microbiologic data. Antifungal therapy with amphotericin B or voriconazole for invasive mold Bronchoscopy and surgery if indicated.*
KEY WORDS*: Chronic pneumonia, Clinical manifestations, Diagnosis, and Therapy.*

I. INTRODUCTION

Pneumonia is a common illness affecting approximately 450 million people a year and occurring in all parts of the world[1].It is a major cause of death among all age groups resulting 4 million deaths[1].Rates are greatest in children less than five, and adults older than 75 years[1].It occurs about five times more frequently in the developing world than in the developed world[1].In the United States, as of 2009,pneumonia is the 8th leading cause of death[2].In 2012 the estimated aggregate costs of treating pneumonia in the United States were 20 billion, and in Europe have been estimated at €10 billion[3,4].The countries with greatest burden of disease include India(43 million),China(21million) and Pakistan(10 million).It is a leading cause of death among children in low income countries [5,1].Chronic pneumonia syndrome(CPS) is a pulmonary parenchymal process that can be infectious or noninfectious, has been present for weeks to months rather than for days, and is manifested by abnormal chest radiographic finding or progressive pulmonary symptoms[6].Older debilitated patients are at higher risk for development of chronic necrotizing pneumonia caused by aerobic gram negative bacteria [7].Racial and genetic characteristics are increasing recognized as predisposing factors to severe disease manifestations from a variety of pathogens e.g. cavitary tuberculosis in blacks, disseminated coccidioidomycosis is much more likely in darker skinned persons and the Asians[8]. Occupation and hobbies play an important role in the development of CPS, e.g. tuberculosis among health care workers; coccidioidomycosis among desert rock collectors, laboratory technicians, archeologists, construction workers and other exposed to desert dust; histoplasmosis in persons exposed to pigeon or starling roosts[9].CPS is also common among homeless persons, smokers ,alcoholics,IV drug users and persons infected with human immunodeficiency virus (AIDS)[10].Travel history of patients is important.A person extensively traveled in Southeast Asia, who subsequently manifests chronic pneumonia, with roentgenographic abnormalities those of tuberculosis or pulmonary mycosis may be suffering from melioidosis [11].Diagnosis include laboratory studies, chest radiographic, and high- resolution computed tomography (HRCT) [12]. Frequently causes of chronic pneumonia include bacteria,fungi and protozoa.Empirical therapy is advisable, the choice of antimicrobial agents must be based on the available epidemiologic, clinical, radiographic and microbiologic data [6].Paper reviews the current literature, clinical presentations, diagnosis and therapy of chronic pneumonia.

II. ETIOLOGIC AGENTS

The infectious causes of chronic pneumonia can be divided into two main groups :(1)agents that typically cause acute pneumonia and are unusual cause of chronic pneumonia and(2) infectious agents that typically cause chronic pneumonia. Among these agents that typically cause acute pneumonia, anaerobic bacteria, *Staphylococcus aureus, Haemophilius influenza*, the Enterobacteriaceae, and *Pseudomonas aeruginosa* are the organisms most likely to produce a persistent chronic pneumonia. This is usually a chronic necrotizing process that most commonly occurs in patients with significant underlying disease(e.g.alcholism, diabetes mellitus,

intracthoraxic malignancy, chronic obstructive pulmonary disease),hospitalized patients, those requiring long term ventilator assistance, patients with chronic swallowing and reflux disorders, and others at risk for recurrent aspiration, such as patients with Parkinson's disease[13].Acute pneumonia caused by most viruses or by *Streptococcus pneumoniae*, *Mycoplasma pneumonia*, *Legionella* species, *Coxiellaburnetti*,or *Chlamydophila pneumoniae* rarely progress to a chronic pneumonia[14].

Chronic pneumonia is caused by bacteria, viruses,fungi and parasites.In the otherwise healthy host, the most considerations are tuberculosis and nontuberculous mycobacteria [15,16].the endemic fungal infections including histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis[17-19],in their geographic areas other mycoses e.g., cryptococcosis[20[],mixed aerobic and anaerobic bacterial infections, and actinomycosis [21,22].Classic opportunistic infections, including nocardiosis and aspergillosis [23,24].In persons with acquired immunodeficiency syndrome(AIDS),these same infections are seen[18].Furthermore, in AIDS patients, chronic pneumonia may be caused by *Rhodococcusequi* or *Pneumocystitis jirovecii*(formerly *P.carinii*) or by such noninfectious disorders as Kaposi's scarcoma, lymphoma, and nonspecific interstitial pneumonitis [25].Protozoan and worms infections are uncommon causes of chronic pneumonia, but they are important considerations for those live in or have traveled to areas in which these agents are endemic[6].

III. CLINICAL MANIFESTAIONS

There are many causes of chronic pneumonia, and no single symptom complex is common to all causes. Often, nonspecific and constitutional symptoms, including fever, chills, and malaise, are present initially, followed by progressive anorexia and weight loss, indicating chronic illness Pulmonary symptoms may be present early but frequently appear later in the course of the illness. Any patient with a prolonged illness and nonspecific constitutional complaints plus pulmonary symptoms-including a new or persistent cough, sputum production, hemoptysis, chest pain(especially pleuritic pain),or dyspnea-deserves medical evaluation, including a chest roentgenogram and, when findings on routine chest radiographs are nonspecific and suggestive of a chronic parenchymal process, a computed tomography(CT) examination of the chest[6].

Evidence of extra pulmonary involvement should be explored with each patient. For example, chronic pneumonia with skin lesions should suggest coccidioidomycosis, blastomycosis, or in the appropriate epidemiologic setting,paracoccidioidomycosis. Similarly cryptococcosis,nocardiosis,and Kaposi's sarcoma should be important consideration for skin lesions in patients with AIDS or other conditions associated with significant impairment of cell-mediated immune function. Mucous membrane lesion should raise the possibility of histoplasmosis, paracoccidioidomycosis, Kapsoi'ssarcoma. Monoarticular or poyarticulararthritis, polyarthralgia,or localized bone tenderness or pain may indicate systemic vasculitis. A history of chronic pneumonia with persistent headache and abnormal cerebrospinal fluid should raise the suspicion of tuberculosis, cryptococcossis, orcoccidioidomycosis involving the lungs and central nervous system[6].The presence of focal neurologic signs and symptoms is strong clinical evidence for a space-occupying lesions in the central nervous system; such finding in a patient with a cavitary infiltrate seen on chest radiograph suggest the possibility of a brain abscess associated with chronic suppurative lung disease caused by microaerophilic or anaerobic bacteria, or nocardiosis [19]. Similarly ,the triad of skin nodules, pulmonary nodules, and central nervous system abnormalities suggests lymphomatoid granulomatosis[26].

Additional signs of chronic pneumonia. Although the findings on physical examination of the chest are usually not helpful in differentiating specific causes of the chronic pneumonia, the presence of generalized wheezing or other signs of bronchospasm, in the absence of underlying lung disease, indicates an asthmatic component to the pulmonary illness and raise the possibility of a disorder causing both pneumonia and asthma, such as extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis, or allergic rhinitis or granulomatosis(Churg-Strauss syndrome).Similarly, localized wheezing signs suggest the presence of an endobronchial obstructing lesion. The findings of tachycardia, cardiomegaly, gallop rhythm, and ankle edema provide evidence of cardiac disease and suggest that the pulmonary symptoms signs result at least in part from cardiovascular causes [6].The presence of skin lesions, clubbing, cyanosis, or phlebitis is not specific for single pulmonary disorder but may help narrow the differential diagnosis, especially when considering along with other clinical and epidemiologic information. The presence of abnormal liver function, lymphadenopathy, hepatomegaly, and/or splenomegaly with chronic pneumonia suggest a systemic disorder involving the reticuloendothelial system, such as sarcoidosis, chronic disseminated histoplasmosis or tuberculosis [6].

IV. DIAGNOSIS

Laboratory workout can provide important clues to diagnosis. Pancytopenia suggests military tuberculosis, disseminated histoplasmosis, or myelophthisic disorder such as metastatic tumor involving the bone marrow. Isolated anemia is commonly associated with chronic pneumonia and is not particularly helpful in discerning a cause. A normal leukocyte count does not exclude infection. In particular, chronic fungal pneumonia may be

associated with a normal or minimally elevated leukocyte count [6]. Leukopenia or lymphopenia should raise the suspicion of a suspicion of an HIV. In addition, leukopenia is consistent with diagnosis of sarcoidosis, systemic lupus erythematosus , tuberculosis, histoplasmosis or neoplasia. Aleukomoid reaction is nonspecific, and may be seen in disseminated mycobacteriosis and mycoses. Leukocytosis with polymorphonu clear cell predominance is suggestive of, but not specific for, a bacterial cause, including actinomycosis[6}
Routine laboratory tests that measure the function of other organs may provide more helpful information. Liver function test(LFT),including bilirubin, alkaline phosphatase, and serum aspartate aminotransferase determinations and prothrombin time, should be performed for most patients. Urinalysis, with particular analysis to urinary sediment, plus tests of renal function including measurement of blood urea nitrogen and creatinine, should also be done. Abnormalities of liver function (especially elevated enzymes levels), kidney function, or both should raise suspicion of disorders that are not limited to lung but are known to involve multiple other organs, including the liver and kidney. Such disorders include disseminated histoplasmosis and disseminated mycobacteriosis as well as the vasculitides, sarcoidosis and certain neoplastic diseases, especially the lymphoproliferative disorders [6].
In a patient with an abnormally low serum globulin level, a quantitative serum immunoglobulin determination should be obtained to evaluate for common variable immunodeficiency disorder or other disorders associated with hypogammaglobulinemia. Studies that should be performed in patients with suspected vasculitis include serologic tests for antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic autoantibodies((C-ANCAs),C-reactive protein, and erythrocyte sedimentation rate. In addition, measurement of serum angiotensin-converting enzyme may be useful, although it is nonspecific test for which levels are increased in patients with number of granulomatous disorders, including 30% to 80% of patients with sarcoidosis [27].

Radiographic studies. The chest radiograph, including a posteroanterior and a lateral film is a reasonable screening procedure, but a high resolution CT(HRCT) provides invaluable information[28].Occasionally, magnetic resonance imaging (IMR) is helpful ,particularly in the evaluation of noninfectious causes of chronic pneumonia.Position emission tomography (PET) scanning(flurodeoxyglucosePET),which measures metabolism by glucose uptake has often proved disappointing in distinguishing malignant from infectious lung lesions[29].Typical radiographic findings may provide clues to specific diagnoses. For example, demonstration of of anterior mediastinal involvement argues strongly in favor of neoplasia, including lymphoma and metastatic carcinoma, as the cause of chronic pneumonia syndrome, and argues against an infectious cause[6].Tuberculosis and nontuberculos mycobacterial diseases , histoplasmosis, coccidiomycosis, sporotrichosis, paragonimiasis, and the pneumoconiosis, especially silicosis, are characteristically associated with fibrocavitary disease-a contracted area of lung with linear fibrosis, nodular or rounded densities, and cavitation. In addition, mycobacterial diseases, histoplasmosis, and silicosis characteristically involve the upper lobes .Many experts believe that anterior segment upper lobe involvement argues strongly against tuberculosis as a cause. A thin walled cavity is suggestive of coccidioidomycosis, sporotrichosis, or paragonimiasis, whereas thick walled cavity surrounded by an area of pneumonitis is more typical of tuberculosis, other mycobacterial infection, histoplasmosis, aspergillosis, melioidosis, nocardiosis, actinomycosis, pyogenic lung abscess ,sequamous cell carcinoma, and lung disease caused by *Rhodococcusequ.* Cavitation is seen but is less common in blastomycosis and cryptococcosis[30].
Mediastinal and/ or hilar lymph node calcification and occasionally parenchymal calcification, is typical of tuberculosis,histoplasmosis, and coccidioidomycosis but is rare in actinimycosis, nocardiosis,blastomycosis,and crptococcosis.Abscess of chest wall or osteomyelitis of rib adjacent to the pneumonia or pleural effusion(empyema necessitans) may be seen in actionmycosis, nocardiosis,, and tuberculosis.Although these radiographic mamifestations of selected pulmonary diseases are typical in most patients, experience during the AIDS pandemic has shown that pulmonary diseases in these patients may be highly typical in radiographic appearance and clinical course[31,32].

Significant radiographicfindings. In all patients with radiographic evidence of localized infiltrates or cavitation, examination of the sputum is essential. This is in striking contrast to the questionable value of sputum in setting of an acute community acquired pneumonia [33,34]..The specimen must be a representative sample-that a deep coughed specimen. Microscopic examination of sputum should include :(a) Gram staining for bacteria and actinomycetes(b) Acid fast stain for mycobacteria and modified acid fast stain for nocardia(c)Wet mount for fungi and eggs of *Paragonimus* (calofluor white potassium hydroxide for preparation with phase contrast may enhance detection of fungi) (d)Cytologic preparations for neoplastic cells, eosinophils, and fungi. Expectorated sputum should also be sent to microbiology laboratory for culture of bacteria. Newer diagnostic techniques (e.g., rapid culture techniques, molecularprobes, and antigen detection assays, and the enzyme-linked immunosorbent assay(ELISA) can be used in rational and thoughtful manner to facilitate laboratory diagnosis. In particular, the development of newer polymerase chain reaction (PCR)-based

diagnostics many of which have the ability to perform screening for multiple pathogens on one specimen. Nucleic acid-based tests for detection of *M.tuberculosis* are commercially available and diagnostically helpful[35,36].Tuberculin skin test with purified protein derivatives(PPD) is the single most important test for the detection of nontuberculous mycobacteria. Serologic tests for HIV should be performed for all patients with unexplained chronic pneumonia. Complement fixation tests for antibody to Coccidioides species. Serum capsular antigen may detected in as many as 50% of patients with pulmonary cryptococcosis; a greater proportion of patients with extra pulmonary disease will have positive serum cryptococcal antigen[37].*Histoplasma* antigen in serum or urine is helpful in disseminated histoplasmosis but uncommonly positive in infection confined to the lung, especially in non immunocom promised patients. The serum Platelia ELISA galactomannan assay for early diagnosis of early active invasive aspergillosis has proven useful hematologic malignancy and stem cell transplantation patients, but its usefulness as a diagnostic assay in other patients is less well established. More recently this assay has been advocated for use in bronchoalveolar lavage(BAL) and may be more sensitive than the serum assay if identifying patients with probable invasive aspergillosis[38,39].Among patients with suspected tuberculosis but with negative culture and histologic studies, the qunatiFERON-gold assay may be useful adjunct to skin testing for diagnosis[40].

Invasive procedures[6].Certain clinical situations dictate a more aggressive diagnostic approach. In patients who are unable to raise sputum spontaneously and in who attempts to induce sputum production are unsuccessful. Invasive procedures may be necessary. Fiber optic bronchoscopy is usually the initial procedure. It is diagnostically helpful when accompanied by BAL, with appropriate microbiologic and histologic studies[35].Analysis of BAL fluid may increase the diagnostic yield of bronchoscopy, especially in immunocompromised persons such as patients with AIDS and suspected opportunistic infections or patients with suspected noninfectious causes of chronic pneumonia[41]. Transbronchial biopsy can be helpful in patients with diffuse pulmonary infiltrates. In a patient with extensive pleural involvement, thoracentesis and pleural biopsy(or rigid throracoscopy is selected situations) may be more helpful diagnostically than bronchoscopy[42].In some situations, open lung biopsy is the procedure of choice for patients with interstitial lung disease and for immunosuppressed patients with unexplained pulmonary disease because of large sample size, the expediency of diagnosis, and the safety of the procedure[41].In contrast, in other institutions with experienced operators, CT guided transthoracic fine-needle aspiration(FNA) of solid lesions in the lung, particularly those near the pleura, can be diagnostic[43].In patients with adequate ventilator reserve, video assisted thoracoscopy(VATS) is preferred to open lung biopsy and is associated with low risk of complications and high sensitivity. VATS requires a chest tube be placed postoperatively [42].

Radiographic evidence with diffuse pulmonary infiltration and fibrosis [6].In patients whose chest radiographs show predominantly diffuse infiltrative patterns of either the alveolar or interstitial type, pulmonary function studies may be of greater importance[44].Studies that may be especially useful in this group of patients include the following:(1)arterial blood gas studies and exercise oximetry(2)tests of pulmonary function, including spirometry measurements, measurements of lung volume, and measurement of diffusion capacity (3)studies on sputum, microbiologic and cryptologic(4)lung biopsy-the procedure of choice to make an accurate morphologic diagnosis(transbronchial biopsy via fiber optic bronchoscope, open ling biopsy or VATS)[45].

V. THERAPY

In many patients no causative agent is identified on the basis of initial stains and cultures, and definitive diagnosis must await the completion of serologic, histologic, and bacteriologic studies as well as other diagnostic tests. In such situations, if immediate empirical therapy is advisable, the choice of antimicrobial agents must be based on the available epidemiologic, clinical, radiographic, and microbiologic data [6].If a patient has a more chronic indolent illness, is stable, and does not require immediate empirical therapy, a methodic and through diagnostic evaluation is the initial priority. In a patient with bilateral upper lobe cavitary disease in whom the initial microscopic examination are nonrevealing, the leading considerations include tuberculosis, histoplasmosis, and cocciodioidomycosis. If such patient has a positive tuberculin skin response, tuberculosis should be presumed to be the diagnosis until proven otherwise, and the patient kept in respiratory isolation until the diagnosis can reasonably be excluded[6].Similarly empirical antifungal therapy, usually with an amphotericin B formulation(or voriconazole if invasive mold disease is suspected).may be indicated in an HIV-infected or other immunocompromised patient with severe or rapidly progressing chronic pneumonia. because fungal pulmonary diseases in this setting can be fatal[6].

Therapy with corticosteroids. The treatment with glucocorticosteroids in the treartment of a patient with chronic pneumonia is controversial. If the cause of the illness is an infectious agent, particularly a bacterium or fungus, steroids are rarely indicated. However; some experts advocate a short course of glucocorticosteroid

therapy for patients with advanced pulmonary tuberculosis and severe inanition. Generally. cortocosteroids are beneficial in chronic pneumonia from noninfectious causes, such as the vasculitides [26], sarcoidosis [46], chronic eosinophilic pneumonia[47],radiation injury[48],bronchiolitis obliterans organizing pneumonia[45],and many of the fibrotic lung diseases, including chronic hypersensitivity pneumonitis(along with avoidance of exposure to the offending antigen[49].

Bronchoscopy and Surgery[6].Bronchoscopy is frequently used as a therapeutic adjunct, especially for patients who have tenacious secretions that cannot be raised by noninvasive techniques. In other patients, mucus plugs or foreign bodies may predispose to atelectasis and chronic pneumonia, and therapeutic bronchoscopy may be necessary to expand the collapsed lung. Surgery plays a limited role in the treatment of chronic pneumonia. Lobectomy or pneumonectomy should be considered in patients with chronic destructive pneumonia, multiple macroabscesses or microabscesses involving an entire lobe or lung, and a ventilation-perfussion scan indicating nonfunction of the involved lung(e.g. Pulmonary gangrene)[50].Thoracotomy may also be indicated to decorticate the pleura in patients with significant pleural reaction and resultant lung disease[6].

VI.CONCLUSION

Chronic pneumonia syndrome (CPS) is a pulmonary illness with 5 million deaths worldwide. CPS is more common in developing than developed countries. Despite the advancement in patient care, outcome remains poor. Future research should focus on early diagnosis and early treatment for better outcome.

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